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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,119	01/12/2001	Sarah S. Bacus	MBHB01-034	1978

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/760,119	BACUS, SARAH S.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2 and 4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 2 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Jan 22, 2007 has been entered.

Claim 1 has been amended. Claims 1, 2 and 4-6 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that the instant invention has the effective priority date of January 12, 2001 for the reasons set forth in the Office action of October 27, 2005.

Claims 1, 2 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites in section c) staining the first and second tissue samples with one or more of a multiplicity of stains that are either X-Gal, or a detectably labeled antibody against the biological markers of p21, p27, p16 or TGF-beta, or X-Gal and said detectably labeled antibody. Claim 1 recites in section e) "determining whether expression of the biological marker was increased". This final method step does not take into account the cells that were stained by X-Gal and correlation of staining by X-Gal with exposure to the cancer chemotherapeutic agent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 rejected under 35 U.S.C. 102(b) as being anticipated by Kopp et al (Cancer Research, 1995, Vol.55, pp. 4512-4515, reference of the IDS filed February 17, 2004)

Claim 1 is drawn to a method for determining a response to administration of a cancer chemotherapeutic agent to an individual comprising a) collecting a first tissue or cell sample from the individual before exposure to a cancer chemotherapeutic agent, b) collecting a second tissue or cell sample from the individual after exposure to the cancer chemotherapeutic agent, c) staining the first and second tissue samples with one or more of a multiplicity of stains that are either X-Gal, or a detectably labeled antibody against the biological markers of p21, p27, p16 or TGF-beta, or X-Gal and said detectably labeled antibody, d) measuring the optical density of the stained cells , wherein the stained cells are illuminated with a light having a wavelength absorbed by the stain, and e) determining whether expression of the biological marker was increased following exposure to the cancer chemotherapeutic agent. Claim 2 embodies the method of claim 1 wherein the detectable labeled is a chromagen or a fluorophore. Claim 4 embodies the method of claim 1, wherein the amount of biological marker protein is determined by an ELISA assay.

Kopp et al disclose a method of determining a response to the administration of tamoxifen to individuals having metastatic breast cancer, comprising taking a blood sample (page 4512, second paragraph under "Patients and Methods") both before and after treatment with tamoxifen(page 4513, "TGF-B2 in Plasma Levels before Tamoxifen Therapy" and "TGF-B2 Plasma Levels under Treatment with Tamoxifen over 12 Weeks") and measuring TGF-Beta2 in plasma obtained from said blood samples by means of an ELISA assay, wherein the TGF-beta2 was labeled with an anti-TGF-beta2 antibody bound by a phosphatase labeled anti-rabbit antibody (pp. 4512-4513, "Determination of TGF-Beta2 in Human Plasma"), thus fulfilling the specific embodiment of claim 2 requiring a chromogen. The optical density was measured on a ELISA reader at 405 nm, thus fulfilling the specific requirement of section d) of claim 1. Kopp et al disclose that TGF-Beta2 levels increased in patients who responded to treatment within 2-6 weeks after the start of tamoxifen, but that patients who did not respond to tamoxifen did not show this early increase, and in some cases of these non-responding patients, the increase in TGF-beta2 was noted much later (page 4513, second column, lines 12-19). It is noted that the

collection of a blood sample fulfills the specific limitation of claim 1 regarding a "cell sample" from an individual.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) in view of Kopp et al (Cancer Research, 1995, Vol.55, pp. 4512-4515

Park et al teach that the chemotherapeutic agent, hydroxyurea, induces a senescence-like phenotype in human erythroleukemia cells. Park et al teach the staining of untreated and hydroxyurea treated cells with X-Gal (page 456, line 6 under "SA-B-galactosidase staining"). Park et al teach the induction or increase of p16, p21, and p27 by hydroxyurea using Western blots and anti-p16, anti-p21 and anti-p27 antibodies labeled with a chemilumiescent substrate and detection with an enhanced chemiluminescence detection system (page 456, second column, under "Western blotting analysis", Figure 5 and page 459, lines 23-27) which fulfills the specific embodiment of claim 1 section d. Park et al teach that prolonged treatment of the cells caused cellular senescence as determined by SA Beta galactosidase staining while short term treatment with hydroxyurea caused differentiation (page 458, second column, lines 10-16 under "Discussion"). Park et al suggest the determination of hydroxyurea induced senescence other types of tumor cells and the clinical interest in using hydroxyurea or any other agent which includes senescence in tumor cells for cancer therapy (page 459, last 8 lines). Park et al does not demonstrate the induction or increase of p21, p16 or p27 in a second tumor sample or blood sample taken from a patient after treatment with hydroxyurea or other senescence inducing agent, wherein an increase in p21, p16 or p27 levels is relative to a first tumor sample or blood sample taken from the patient before treatment.

Kopp et al teach the measurement of TGF-Beta2 levels in a patient both before and after chemotherapeutic treatment in order to eliminate the inter-individual differences between patients that would be present if only the post-treatment value was used (page 4512, second column, lines 8-11).

It would have been prima facie obvious at the time the claimed invention was made to assess the increase in levels of p21, p16 or p27 from tumor samples taken from patients or blood samples taken from patients having erythroleukemia as markers of senescence. One of skill in

the art would have been motivated to do so by the suggestion of Park et al that hydroxyurea or other cellular senescence inducing agent can be used for a generic cancer therapy. One of skill in the art would have been motivated to use a relative value of increase based on the difference between the post-treatment value and the pre-treatment value in order to overcome individual differences between patients as taught by Kopp et al.

Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) and Kopp et al (Cancer Research, 1995, Vol.55, pp. 4512-4515) as applied to claims 1 and 4 above, and further in view of Bentsen et al (U.S. 6,372,895) and Pinkel et al (U.S. 5,665,549).

Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is performed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is performed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having difference absorptions and transmittance properties so that each signal is specific for one of a multiplicity of stains.

The combination of Park et al and Kopp et al render obvious claims 1 and 4 for the reasons set forth above. The combination does not teach image analysis or the specific limitations of claim 6.

Bentsen et al teach an image analysis system comprising emission optical filters, collection optics , focusing optics and an optional light guidance system configures to receive multiple emission signals from each fluorogenic enzyme substrate (column 25, lines 51-67) as well as a beam-splitter (column 26, lines 54-58). Bentsen et al teach the conjugation of fluoresent labels to antibodies (column 21, line 55 to column 22, line 2).

Pinkel et al teach that an image analysis system can be used to enhance or accurately quantitate the intensity differences relative to background staining differences for more accurate and easier result interpretation (column 23, lines 16-20).

It would have been prima facie obvious at the time the claimed invention was made to employ the image analysis system of Bentsen et al for the detection of fluoresently labeled antibodies which bind to p21, p16 and p27. One of skill in the art would have been motivated to do so by the teachings of Bentsen et al regarding the image analysis system for the detection of

fluorescently labeled antibodies and the teachings of Pinkel et al regarding the increased accuracy and ease of interpretation afforded by the use of an image analysis system.

All other rejections and objections as set forth or maintained in the prior Office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A Canella, Ph.D.
4/17/2007

KAREN A. CANELLA PH.D
PRIMARY EXAMINER